Thimerosal-Autism Case-Control Study

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Background

- High doses of methylmercury exposure cause a range of neurologic impairments (Harada, 1995; Bakir et al.,1973; Marsh et al., 1980
- Low dose methylmercury exposure can also lead to more subtle neurodevelopmental deficits (Grandjean et al., 1998)
- Thimerosal contains approximately 49% ethylmercury.
- Previous ACIP recommended immunization schedule could lead to Hg exposure exceeding EPA's safety limits for methylmercury exposure (Ball & Ball, 2001)
- Since 2001, all U.S.-licensed vaccines recommended for children 6 years of age and younger have been manufactured in thimerosal preservative-free formulations, with the exception of inactivated influenza vaccines.

Background

- Ecologic studies have found that autism rates continued to increase even after thimerosal was removed from vaccines
  - Madsen et al., 2003
  - Stehr-Green et al., 2003
  - Fombonne et al., 2006

- Autism Cohort Study (Hviid et al., 2003)
  - Population based cohort study of 470,000 children born between 1990-1996
  - No association between thimerosal exposure and risk for autism

- Verstraeten et al (2003)
  - Large observational cohort study within VSD found no statistically significant association between thimerosal exposure and autism

Background

- IOM Vaccines and Autism (2004)
  - "Evidence favors rejection of a causal relationship between thimerosal containing vaccines and autism"
  - "Many of the epidemiological research recommendations of the Committee's 2001 report on thimerosal and [neurological developmental disorders] are either under way or have been completed"
  - Available resources should be focused on causes and treatments of autism.

Protocol Development

- Abt Associates Inc. successfully competed for contract competition in 2002 for protocol development
- Input in developing protocol included:
  - CDC staff
  - Principal investigators from Vaccine Safety Datalink-participating managed care organizations (MCOs)
  - Independent, external expert consultants
- The final analysis plan was approved by each of the external expert consultants

Primary Research Question

- Is there an association between the diagnosis of autistic disorder and level of Hg exposure from vaccines and immunoglobulins?

Methods: Design and Population

- Study design: 3:1 matched case control design
- Mothers recruited from 3 HMOs
- Children's age 5 - 11 years (birthdates 1/94 – 12/99)
- All subjects received vaccines during period when thimerosal containing vaccines were used frequently

Methods:Data Collection

- Parent Interview
  - Administered to both cases and controls
  - Extensive data collection on confounders, such as family demongraphics, medical history, etc
  - Social Communication Questionnaire (SCQ), administered only to controls as a screening tool
    - SCQ Positive Control Children – excluded from the study

Methods:
Hg Exposure Periods

- Prenatal Hg exposure
- Hg exposure birth through 28 days of life
- Hg exposure 1 through 7 months of age

Methods: Clinical Case Assessment

- Clinical interviews with mother
  - Autism Diagnostic Interview-Revised (ADI-R)
  - Regression Interview
- Clinical assessment of case children
  - Autism Diagnostic Observation Schedule (ADOS)
  - Measures of cognition
    - Raven's Colored Progressive Matrices
    - Mullens Scales of Early Learning

Methods: Sample Size & Power

- Power Calculations for Autism Spectrum Disorders (ASD)
  - Sample of 320 ASD and 960 matched controls
    - Prenatal exposure
      - 80% power to detect OR 1.8 per 12.5 ug increase
    - Birth to 28 days exposure
      - 80% power to detect OR 1.9 per 12.5 ug increase
    - Birth to 7 months exposure
      - 80% power to detect OR 1.1 per 12.5 ug increase

Current Status

- Total Confirmed Autism Spectrum Disorders Cases: 233
- Target numbers
  - 27 additional AD children
  - 60 additional ASD children
- Complete data collection by 7/2007